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| EXAMINER | |
|---|---|
| SULLIVAN, DANIEL M | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/966,768 | VAN DER KOOY ET AL. | |
| | Examiner | Art Unit | |
| | Daniel M. Sullivan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-11,13-17,20-22,25-27,29,30,33-38,41,42 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-17,20-22,25-27,29,30,33-38,41,42 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This Non-Final Office Action is a reply to the Paper filed 20 May 2005 in response to the Non-Final Office Action mailed 17 November 2004. Claims 1-11, 13-17, 20-22, 25-27, 29-38, 41, 42 and 47-49 were considered in the previous Office Action. Claims 31 and 32 were canceled and claims 4-6 were amended in the 20 May Paper. Claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42 and 47-49 are pending and under consideration.

### *Response to Amendment*

Rejection of claim 31 is rendered moot by the cancellation thereof.

Rejection of claims 4-6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments thereto.

### *New Grounds for Rejection*

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13-17, 20-22, 25-27, 29, 30, 33-38, 41, 42 and 47-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mouse primitive neural stem cell and a method of making and using a primitive neural stem cell wherein

the primitive neural stem cell are produced from a culture of mouse ES cells, does not reasonably provide enablement for a neural stem cell, method of making or method of using a neural stem cell wherein the cell is produced from any species of ES cell other than mouse. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

*Nature of the invention and Breadth of the claims*: The claims are directed to a method of making a primitive neural stem cell comprising culturing ES cells at a low density in a serum-free and feeder-layer free media comprising leukemia inhibitory factor and allowing the ES cells to differentiate to primitive neural stem cells. Claims are also directed to primitive neural stem cells produced by the method, or any other method, and methods of using the primitive neural stem cell to screen for modulators of primitive neural stem cell differentiation.

The claims broadly encompass methods of making primitive neural stem cells wherein the starting material can be embryonic stem cells from any species of animal and the product claims embrace primitive neural stem cells of any species.

*Amount of direction provided by the inventor and existence of working examples*: With regard to working examples, the specification demonstrates that a single line of mouse ES cells (*i.e.*, R1) cultured in the presence of LIF and the absence of serum at a density below which embryoid body formation occurs assume a partially differentiated state which Applicant's refer to as a primitive neural stem cell (see specially Example 1). The specification identifies the primitive neural stem cells of the invention as "LIF dependent cells" having a much higher degree of pluripotent fates than do the definitive neural stem cells isolated in similar *in vitro* neurosphere assays from embryonic or adult brain (page 15, line 21-24). In Example 2, the specification teaches that the primitive neural stem cells express the marker nestin (page 27, lines 11-12) Emx2, HoxB1 (page 29, lines 23-25), and GATA4 (page 30, line 10) and fail to express Oct-4 (page 27, lines 21-22), Six3 and Otx1 (page 29, lines 27-28). In Example 3, the specification presents evidence indicating that although LIF is critical for the early transition of ES cells into colony-forming neural stem cells, it may act primarily as a permissive factor to maintain cell survival under minimal conditions (first full paragraph on page 31).

The specification fails to provide any guidance with regard to extending the findings obtained with mouse ES cells to any other species of animal or mammal. Thus, the specification leaves to the skilled artisan seeking to make and use the full scope of the claimed invention with the task of extending the methods disclosed in the application such that one would be able to make primitive neural stem cell from any species of animal.

*State of the prior art and level of predictability in the art*: The art teaches that the properties of embryonic stem cells are highly species specific and that processes developed using a mouse ES cell cannot be generically applied to all ES cells. In particular, the art recognizes that

ES cells isolated from different species exhibit significantly different properties. Wheeler (US Patent No. 5,942,435) describes many problems encountered in extending successes obtained with mouse ES cells to other mammalian species. For example, Wheeler teaches that attempts to establish useful stem cells from pigs and sheep produced disappointing results (column 2, third full paragraph; column 3, fifth full paragraph); and teaches that a problem "in extrapolating from mice to ungulates, such as swine, is that exactly analogous stages do not exist in the embryos of mice and ungulates..." (column 4, second paragraph). Thus, establishing ES cell lines from other species of mammals or animals having properties that are analogous to the mouse ES cells used in the methods of the instant application is highly unpredictable.

Of particular import in the instant case, because the primitive neural stem cells of the instant application are identified as "LIF dependent", is the distinct effects of LIF on ES cell lines obtained from different species of animals. Sato *et al.* (2004) *Nat. Med.* 10:55-63 teaches that the ability of LIF signaling to support self-renewal of murine ESCs does not extend to human ES cells, which differentiate in spite of the presence of LIF (see especially the second paragraph in the left column on page 61). Humphrey *et al.* (2004) *Stem Cells* 22: 522-530 states, "[t]he factors and signaling pathways that regulate 'stemness' in human embryonic stem (hES) cells remain to be elucidated" (left column of the abstract) and particularly points out that "stimulation of human and mouse ES cells with LIF and IL-s resulted in a robust phosphorylation of the STAT3 transcription factor. However, the cytokine-treated hES cells proceeded to differentiate, even in the presence of gp130-depenedent signaling, with the progressive loss of markers of pluripotency" (paragraph bridging pages 527-528). Thus, Humphrey teaches that, activation of the signaling pathway that is identified in the instant

application as critical to establishing the primitive neural stem cell of the invention has dramatically different effects in mouse and human ES cells. These teachings clearly show that experiments performed using LIF in mouse ES cells cannot be readily extended to other species of mammal or to humans in particular.

*Relative skill of those in the art and quantity of experimentation needed to make or use the invention*: Although the relative level of skill in the art is high, the skilled artisan would not be able to make the full scope of what is presently claimed without undue experimentation. The claims are extremely broad, covering methods of making and using primitive neural stem cells established by culturing ES cells from any species at low cell density in a serum-free and feeder-layer free media comprising LIF. Claims also cover primitive neural stem cells of any species of animal made by any means. However, the art teaches that ES cells obtained from different species of mammal, let alone animal, exhibit unique properties that are not adequately modeled by mouse stem cell lines. In particular, the art teaches that the response of ES cells to LIF and activation of LIF signaling is not uniform across mammalian species. Therefore, the art recognizes that the developmental response of ES cells to any given manipulation, and to the presence of LIF in particular, is highly unpredictable across different species of animal. In spite of this, the teachings of the instant application are limited to producing primitive neural stem cells from a single mouse ES cell line. There is no disclosure of which species of ES cells, other than mouse, would respond to the disclosed method in the same way as mouse ES cells and there is no disclosure of what additional manipulations would be required to enable the skilled artisan to generally produce a primitive neural stem cell from any species of animal.

In view of the undeveloped and unpredictable state of the art and the absence of guidance with regard to practicing the invention with ES cells other than mouse ES cells, the skilled artisan would have to engage in undue experimentation to practice the invention commensurate with the scope of the claims. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking a fully enabling disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25-27, 29, 30, 48 and 49 are rejected under 35 U.S.C. 102(b) as anticipated by Dinsmore *et al.* (1998) *Theriogenology* 49:145-151.

The instant claims are directed to an isolated primitive neural stem cell, which is disclosed in the application as an LIF-dependent cell exhibiting markers consistent with neural cell differentiation.

The specification also teaches, "the present invention describes a previously unidentified primitive neural stem cell stage in the neural lineage, that transition between ES cell and neural stem cell" (bridging pages 3-4); and, in Example 8, the specification teaches that high density cultures of mouse ES cells grown in the presence of serum and LIF comprise $Nestin^+$ cells having morphology resembling the $Nestin^+$ cells from he low cell density cultures (*i.e.*, primitive neural stem cells; see especially page 39, lines 22-25).

Dinsmore *et al.* teaches culturing a mouse ES cell line in the presence of serum and LIF (see especially the third paragraph on page 146). Dinsmore *et al.* further teaches that the cells can be induced to differentiate into neuronal cells (see especially the first paragraph on page 148). In view of the teachings of the instant specification indicating that the claimed cells are an intermediate between ES cell and neural stem cell and that cells having the characteristics of the primitive neural stem cell are present in high density cultures of mouse ES cells, the skilled artisan would conclude, absent evidence to the contrary, that the ES cell cultures of Dinsmore *et al.* comprise isolated primitive neural stem cells, which cells would express the various markers recited in the claims. With regard to claim 49, directed to a sphere colony comprising primitive neural stem cells, Dinsmore *et al.* teaches trypsinizing the ES cell cultures and seeding the cells in Petri dishes such that the cells adhere to each other to form cell aggregates. As the specification provides no explicit definition of a "sphere colony" these cell aggregates are viewed as meeting the limitations of a sphere colony comprising at least one primitive neural stem cell according to the limitations of claim 49.

The Office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989).

"[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

In view of these considerations, the ES cell cultures of Dinsmore *et al.* anticipate the primitive neural stem cells of the instant application. Therefore, the claims are properly rejected under 35 USC §102(b).

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M. Sullivan, Ph.D.
Examiner
Art Unit 1636

DANIEL M. SULLIVAN
PATENT EXAMINER